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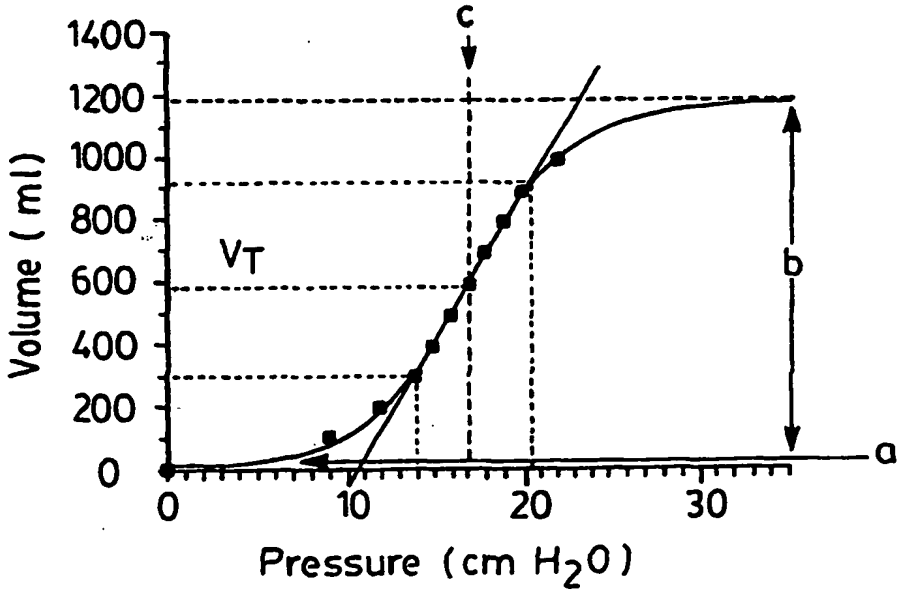

(57) Abstract: The flow of a biological fluid, including ventilation gas and blood, to an organ during controlled life support condition is controlled. For ventilation, a static pressure volume curve for the patient is established in accordance with the Venegas equation, a predetermined pattern of variation ver time of the instantaneous respiratory rate and tidal volume from spontaneously-functioning normal lungs f a mammalian species established, data is selected from the pattern which satisfies a specific relationship with respect to the pressure/volume curve, and the patient is ventilated in accordance with the selected data.

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TITLE OF INVENTION

IMPROVED CONTROL OF LIFE SUPPORT SYSTEMS

FIELD OF INVENTION

The present invention relates to life support systems, in which a biological fluid flows to an organ, and, in particular, to the control of mechanical ventilation and to the control of cardiopulmonary bypass pumps for open heart surgery.

BACKGROUND TO THE INVENTION

Mechanical ventilation is one of the mainstays of modern medicine. Despite ubiquitous use, mechanical ventilation can be associated with deteriorating gas exchange over time in normal lungs (ref. 1). Lung damage can also occur with mechanical ventilation – so called ventilator associated lung injury (VALI) and is most common in patients with acute respiratory distress syndrome (ARDS) (ref. 2). Much attention has been directed to the latter problem and a recently completed National Heart, Lung and Blood Institute (NHLBI) study has shown the advantage of open lung – low tidal volume (V_T) strategies for management of these patients (ref. 3). In this patent application, there is described an optimizing strategy for ventilation of patients with ARDS that can be generalized to control mode ventilation for all patients.

In our U.S. Patents Nos. 5,647,350, 5,941,841 and 6,027,498, the disclosure of which are incorporated herein by reference, we have described a new method of controlling the flow of a biological fluid to an organ, in which the natural variation of such flow is simulated. Specifically described are the control of a mechanical ventilator output to mimic normal breathing of healthy lungs and the control of a blood pump flow output during cardiopulmonary bypass (CPB) to mimic normal pulsatile blood flow from the heart. A pattern of variation over time of the instantaneous flow of a biological fluid to an organ of a mammalian species is established, a variable control parameter for regulation of flow of the biological fluid to the organ is generated in accordance with the pattern, and the flow of biological fluid to the organ is controlled in accordance with the variable control parameter. This mode of ventilation is termed biologically variable ventilation (BVV)

Recently it has been shown that patients with ARDS are better ventilated at a lower tidal volume, namely about 6 vs 12 ml/kg (ref. 3). The choice of 6 ml/kg was somewhat arbitrary, but associated with a plateau pressure of 30 cm H_2O or less.

SUMMARY OF INVENTION

In one aspect of the present invention, there is provided a method of controlling the flow of ventilation gas from a ventilator device to the lungs of a body of a patient during controlled life support conditions. The ventilation gas is the primary source of gas to maintain life support to the lungs.

In this invention, a static pressure/volume curve is established for the patient by any convenient means in accordance with the relationship:

$$V = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

V = inflation volume

P = airway opening pressure

a = lower asymptote volume

b = total volume change

c = pressure at point of maximal compliance

d = value proportional to the pressure range of a straightline portion of the curve

The relationship is the so-called Venegas equation (ref. 4). A predetermined pattern of variation over time of the instantaneous respiratory rate and tidal volume is establishing from spontaneously-functioning normal lungs of a mammalian species.

Data from the pattern is selected which satisfies the relationship $P = V_c \pm V_{1.317d}$ with respect to the pressure/volume curve. The patient then is ventilated in accordance with the selected data.

In more general terms, in another aspect of the invention, there is provided a method of controlling the flow of a biological fluid to an organ during controlled life support conditions. The biological fluid is the primary source of fluid to maintain life support to the organ.

In this aspect of the invention, a static pressure/flow curve is established for the patient by any convenient means in accordance with the equation:

$$F = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

F = organ flow

P = driving pressure

a = lower asymptote flow

b = autoregulated flow

c = pressure at point of maximal conductance

d = value proportional to the pressure range of a straightline portion of the curve

A predetermined pattern of variation over time of instantaneous changes in flow of a biological fluid to a spontaneously-functioning normal organ of a mammalian species.

Data from the pattern is selected which satisfies the relationship $F = \dot{V}_c \pm \dot{V}_{1.317d}$. The flow of biological fluid to the organ during controlled life support conditions then is controlled in accordance with the selected data.

Similar to the above procedure with respect to the lungs, a flow-pressure curve may be established for the whole body or individual organs.

An example of such control of biological fluid to an organ is in controlling the flow of blood by a pump to a body during cardiopulmonary bypass. In this instance, a predetermined pattern of variation over time of instantaneous blood pressure and heart rate of a spontaneously-functioning healthy heart of a mammalian species is established. Data is selected from the pattern which satisfies the above relationship. The flow of blood to the heart of the patient during controlled life support conditions then is controlled in accordance with the selected data.

The following consequences flow from understanding of the model discussed below as set forth uniquely herein:

1. The optimal point about which to ventilate a patient is at the inflection point *c*. Maximal compliance occurs here. Supersyringe or comparable determination of

compliance curves in patients permits determination of V at *c*. Based on the Venegas P-V curve, the V_T at a given PEEP level can be calculated. Patient V_T at point *c* is (V_Tc – V_{PEEP})/ml/kg . The $V_{Tc} \pm V_{1.317d}$ to ventilate a patient can be readily determined (see Figure 1a for an example - from Eq. 4 below, *d* can be shown to be 3.4 cm H_20). The difference between ventilation with BVV and standard control mode can be understood by further study of Figure 1a. Assuming that a 100 kg patient is ventilated as in the NHLBI protocol at 6 ml/kg; in this circumstance V_T would be at point *c*, a fortuitous situation chosen in this example, with the patient ventilated in a monotonous manner at the point of maximal compliance. Ventilation under these circumstances results in recruitment to 600 ml, independent of PEEP settings. Recruitment above this point is lost, so full recruitment of the linear portion of the P-V curve is not obtained. Ventilation at 12 ml/kg in this example is clearly problematic, at a V_T of 1200 ml ventilation occurring at the upper asymptote where the risk of volutrauma is substantial if monotonously delivered at this volume.

2. Ventilation at $V_{Tc} \pm V_{1.317d}$ allows the full linear portion of the P-V curve to be generated. Variable V_T is a consequence of using variable *f* as generated from normal awake breathing with BVV programmed as a volume divider. A characteristic breathing file is shown in Figure 4. The tight correlation between Paw_I and V_T generated from a modulation file, as in Figure 4, is shown in Figure 5. The very high R^2 value in this circumstance suggests that ventilation is occurring within the linear portion of the P-V curve in this example. The use of BVV improves gas exchange in a model of ARDS at PEEP (ref. 9), with ARDS treated with 10 cm H_2O PEEP (ref. 13), reinflation of a collapsed lung after one lung ventilation (ref. 14) and during prolonged anesthesia with healthy lungs (ref. 7). Generating a P-V curve dependent on $V_{Tc} \pm V_{1.317d}$ allows mean V_T to be set as with conventional control mode ventilation, but results in improved gas exchange, maximizing alveolar recruitment, without an increase in mean airway pressure (Paw). The Paw does not increase because of the Gaussian distribution of V_T.

3. The slope of the linear portion of the P-V curve relates to the severity of ARDS, with a depressed slope indicating worsening disease with less compliant lungs. As such, *d* may change as ARDS severity alters with the disease process or

therapy. Changes in *d* can be readily accommodated by altering the 1/f slope of the BVV modulation file (see Figure 3). By altering *d*, changes in compliance with the disease state can be treated and thereby optimize ventilation for each patient with ARDS.

4. The optimal 1/f slope to ventilate normal lungs is unclear but BVV has been shown to improve gas exchange in normal lungs during prolonged anesthesia with a 1/f slope = -2.3 (ref. 7). In normal lungs, the P-V curve has a much steeper slope. As a consequence, *d* is proportionately small. A 1/f slope of approximately -3 has been shown to correlate to *f* variability in normal neonates (ref. 8) and as an index of the diameter-flow relationship in the bronchial tree (ref. 15).

The variable quasi-Gaussian distribution curves utilized herein can be best obtained from normal respiratory data files of awake spontaneously breathing individuals, which may be mammalian, including human, or may be obtained from computer-generated files based on such data. Such files have been labelled normal biological variability. From such data, various standard deviations about mean values can be generated either as: 1) separate modulation files to control the ventilator in BVV mode or 2) by using a generic file which can have the standard deviation altered by ventilator software or by hardware, such as a knob to control magnitude of standard deviation or slope of the $1/f^{\beta}$ frequency plot.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1(a) shows the pulmonary pressure-volume (P-V) curve as an integrated normal distribution. The variables are as discussed herein.

Figure 1(b) shows the normal distribution of airway opening pressure (Pao). This curve is the derivative of dimensionless curve of Figure 1(a). When Pao describes a normal distribution, the P-V curve is generated (the integral of Figure 1(b)). The solid line is a normal distribution. The dotted line is the Venegas (ref. 4) derivative function with $\bar{d}\sqrt{\sigma\pi^{1/4}}$ when volume is normalized to (V-*a*)/*b* and pressure is normalized to (P-*c*)/*d*, as such relationships being described below.

Figure 2 shows the respiratory rate (*f*) frequency vs. *f* (breaths/min). Data were obtained during awake spontaneous breathing and scaled to a mean rate of 20 breaths/min in this Example. There were 654 consecutive breaths analyzed.

Figure 3 is a 1/f noise plot of the data presented in Figure 2. As values deviate from the mean, the probability of variation (difference from mean)^2 decreases. The slope of the line a = -2.15. The steeper the slope the less frequent the rare events, the shallower the slope, the more frequent the rare events at the same variation.

Figure 4 shows a modulation file used to program for biologically variable ventilation (BVV). There are 654 instantaneous breaths shown. The rate has been scaled to 20 breaths/min.

Figure 5 is a graphical representation of tidal volume changes with BVV. The change V_T over time with the above modification file (measured over a 45 breath interval). The BVV module functions as a volume divider, a set minute ventilation is delivered, such that f x V_T is constant. Thus increased f is coupled with decreased V_T and vice versa.

Figure 6 is a graphical representation of peak airway pressure changes with BVV. The P_{PAW} is matched to the V_T delivered in Figure 5.

Figure 7 is a graphical representation of a static P-V curve prepared from data downloaded from a data acquisition system.

Figure 8 is a graphical representation of a diastolic stiffness constant (Kp) verses time period post–CPB (coronary pulmonary bypass). Kp was significantly elevated post bypass with conventional cardioplegia administration, an approximately 100% increase in stiffness. In contrast, Kp remained essentially unchanged with biologically variable administration of cardioplegia, P = 0.003; group x time interaction.

GENERAL DESCRIPTION OF INVENTION

(a) The P-V Recruitment Function:

Venegas et al. have analyzed normalized compliance curves and demonstrated that the pulmonary pressure-volume (P-V) curve can be fit with excellent precision to a modified integrated normal curve (R^2 = 0.997 ± 0.02 (SD)) (ref. 4). Based on their observations, they suggest the standard P-V curve may be thought of as a recruitment function rather than as a compliance curve. Carney et al. provide experimental evidence to support this contention (ref. 5). They demonstrate that increased lung volume with inflation by a mechanical

ventilator is 80% a consequence of recruitment and only 20% due to isotropic expansion.

The equation developed by Venegas et al. has four fitting parameters, *a* to *d*, each with physiological correlates as follows:

$$V = a + b[1 + e^{-(P-c)/d}]^{-1}: \qquad \text{Eq. 1}$$

Where: V = inflation or absolute lung volume

P = airway opening or transpulmonary pressure

a = lower asymptote volume

b = vital capacity or total volume change: upper - lower asymptote

c = pressure at the inflection point (point of maximal compliance)

d = proportional to the pressure range where most of the volume change occurs.

This sigmoidal curve (Figure 1a) is symmetrical with respect to its inflection point *c*. Thus, *c* is the midpoint of volume $b - a$.

(b) The Derivative of the P-V Recruitment Function:

Since Eq. 1 is a form of the integrated normal distribution, its derivative as demonstrated by Venegas et al. has the form:

$$\partial V/\partial P = b[e^{-(P-c)/d}]/d[1+e^{-(P-c)/d}]^2 \qquad \text{Eq. 2}$$

Graphing the dimensionless curve $\partial(V-a)/b$ vs $(P-c)/d$ results in a standard Gaussian distribution. The point *c* is the peak of the bell curve, the true inflection point and the point of maximal compliance (Figure 1(b)). When P = *c* then:

$$c = b/4d \qquad \text{Eq. 3}$$

From this relationship, *d* can be calculated because maximal compliance is defined as the slope of the tangent at point $c = \partial V/\partial P$. Therefore:

$$d = b/4(\partial V/\partial P)_c \qquad \text{Eq. 4}$$

It can also be shown that standard deviation (σ) of the normal distribution is proportional to *d* such that:

$$d = \sigma\pi^{1/2}. \qquad \text{Eq. 5}$$

Thus, *d* is a measure of the standard deviation of the normalized pressure curve.

The implication of the above analysis is that, when change in airway opening pressure (Pao) displays a Gaussian distribution, a sigmoidal P-V curve with lower and upper inflection points is generated as a consequence. As stated in

their article "This observation gives a basis to the intriguing possibility that the sigmoidal shape of the inflation limb of the P-V curve in ARDS could be reflecting the progressive recruitment of alveolar units with a distribution of Pao that follows a normal distribution (ref. 4)." Interestingly, in a follow up article using their curve fitting model to analyze patients with ARDS, Harris et al. state: "There is no physiologic reason why the shape of the P-V curve must have such symmetry (ref. 6)." We contend that their initial observation is correct and that if Pao follows a Gaussian distribution, then a symmetrical P-V curve is mandated mathematically. This result is a consequence of the fact that the antiderivative of the normal distribution (Gaussian Pao) becomes the integrated normalized curve (P-V curve). In essence, when Pao has a normal distribution, this function serves as the algorithm to generate the sigmoidal P-V curve.

Generating P-V curves and fitting to the Venegas equation permits individualized management of patients with ARDS. Calculation of point $c \pm 1.317d$ gives values of Pao whereby ventilation is centered about the point of maximal compliance and defines the range where respiratory system compliance is essentially linear. Ventilation with V_Ts that generate Pao between $c \pm 1.317d$, would minimize the consequences of atelectrauma and volutrauma. Reflection of the Pao range onto the ordinate defines the range of V_Ts that are optimal for ventilation of a patient with ARDS as calculated from their P-V curve. Examination of Figure 1a shows how such an optimal V_T range is calculated. V_T reflected from point $c \pm 1.317d$ is approximately 600 ± 300 ml. Over this range of V_T the linear portion of the P-V curve is generated. During lung inflation, how best to deliver this range of volumes associated with linear compliance? A centering V_T equal to that volume at point c maximizes compliance for an individual patient. Volume recruitment can be maximized by ventilation to $V_{+1.317d}$, the volume associated with the point of maximal change in compliance (P_{mci}) as defined by Venegas, but monotonously regular delivery of such large volumes are deterimental as recently described in the NHLBI study. A Gaussian distribution of V_Ts with mean V_T centered at point c can generate the linear point of the P-V curve without the problems associated with monotonously regular

ventilation. Such a ventilatory strategy is provided by biologically variable ventilation (BVV).

(c) Pao and Biologically Variable Ventilation:

Awake, spontaneous breathing is associated with quasi-Gaussian distributions in respiratory rate (*f*) and V_T. These respiratory variables have been examined in terms of 1/f frequency distribution plots (refs. 7 and 8). The relationship between these two demonstrations of variation in such respiratory data is shown in Figure 2 and 3. The quasi-Gaussian frequency plot of *f* data from awake spontaneous breathing is shown in Figure 2 and the 1/f noise plot is shown in Figure 3. We have used such normal variation in *f* to program a mechanical ventilator to vary V_T and thus Pao (refs. 7 and 9). Under these circumstances, the correlation between V_T and mean inspiratory airway pressure (Paw_I) is shown in Figure 5. We have called a ventilator programmed in such a manner biologically variable ventilation or BVV and is generally and specifically described in aforementioned U.S. Patent No. 5,647,350.

Marini and Ravenscraft have documented the relationship between Paw_I and mean alveolar pressure (P_A)(ref. 10). In the absence of PEEP, both are related to the pressure measured at the airway opening or Pao provided that inspiratory and expiratory resistances are equal. If not the following equation applies:

$$P_A \; Paw_I(T_I/T_T) + V_E/60\cdot(R_E - R_I) \qquad \text{Eq. 6}$$

Where: T_I = inspiratory time

T_T = total respiratory cycle time

V_E minute ventilation

R_E expiratory resistance

R_I = inspiratory resistance

With BVV, V_E remains fixed by design as the ventilator functions as a volume divider with a constant *f* x V_T product. As well, T_I:T_T is designed to remain fixed at 1:3. Disparities in R_E and R_I are not usually clinically important at normal levels of ventilation (ref. 11). With R_E and R_I not different, the second term in Eq. 6 cancels out. At fixed T_I/T_T, P_A and Paw_I are linearly related. Therefore, with BVV, measured Paw_I under most circumstances is an accurate index of Pao. Thus, BVV is a volume cycled control mode ventilator that

generates quasi-Gaussian airway pressures. Appropriate selection of a range of V_Ts based on calculation from the Venegas equation allows ventilation over the linear range of the P-V curve - improving gas exchange and respiratory mechanics in a variety of experimental settings as outlined below.

Using another theoretical model, Suki et al. have demonstrated that the variable end inspiratory pressure with BVV can recruit atelectatic lung units seen with ARDS (ref. 12).

Clearly a variety of strategies can generate the range of V_Ts associated with ventilation over the linear portion of the P-V curve in a patient with ARDS. A number of advantages occur with a Gaussian distribution of V_T:

1. Physiologically normal breathing patterns have a Gaussian distribution for V_T. BVV takes advantage of such naturally occurring breathing frequency distributions (see Figure 2) to generate quasi-Gaussian V_T.

2. A Gaussian distribution of V_Ts can be centered about that V_T associated with maximal compliance for each patient with ARDS. Higher and lower V_Ts within the linear range of pressures are also generated but at steeply decreasing frequency. As the inspiratory P-V curve is linear over this range, airway pressure averaged over time is equal to that seen at point *c*, since the higher pressures associated with volume recruitment are balanced by the lower pressures seen with derecruitment.

3. The distribution of V_Ts is naturally determined from awake spontaneously breathing subjects. A random allocation of V_T - as in white noise - would increase the frequency of pressures at the extreme range of the linear portion of the P-V curve - potentially increasing the risk of atelectrauma and volutrauma. The advantage of a Gaussian distribution of V_Ts is evident with changes in lung compliance with evolving severity of ARDS. With a Gaussian distribution of V_T with BVV, Pao at point $c \pm 1.317d$ does not cause ventilation to occur beyond the upper or lower inflection points, minimizing the risk of atelectrauma and volutrauma.

In summary of this invention, biologically variable ventilation leads to a quasi-Gaussian distribution of airway pressure. A Gaussian distribution of Pao

generates a full sigmoidal pulmonary P-V curve. Understanding the implications of the Venegas equation (both the derivative and the antiderivative or integral form) theoretically explains why BVV is effective. BVV has improved gas exchange in a broad spectrum of experimental conditions. Using the Venegas equation to fit generated P-V curves, in concert with BVV, may improve management of patients with ARDS. Use of BVV at individualized $V_{Tc} \pm V_{1.317d}$ centered about the inflection point *c* may maximize alveolar recruitment without an increased risk of lung damage. In addition, improved gas exchange and respiratory mechanics in healthy patients requiring prolonged ventilation under anesthesia is also possible with BVV.

The above description has referred specifically to an embodiment of the invention concerned with ventilators and to providing improved mechanical ventilation with BVV utilizing the Venegas equation. The same analysis can also be applied to cardiopulmonary bypass (CPB) utilizing biologically variable pulsation (BVP) adapting the Venegas equation to pressure-flow rather than pressure volume, in accordance with another specific embodiment of the invention, as discussed below.

In the broad scope of the invention, the control of the flow of biological fluid to an organ utilizing a biologically variable control parameter can be improved.

Referring to the blood pump embodiment of the invention, we have previously demonstrated improved bypass with our BVP module (refs. 16, 17) as described in USP 5,647,350. An explanation for the nature of the cerebral lesion associated with CPB has also been delineated by us (ref. 18).

The integrated normal curve that describes the P-V curve in the paper by Venegas et al (ref. 14) can also be applied to flow-pressure curves used to describe circulatory beds (see Figure 4 in ref. 17). Thus, generating a $1/f^a$ plot of perfusion pressure, a quasi-Gaussian curve generates the full lower end of the autoregulatory curve of the flow-pressure curve in the brain and the lower end of the flow-pressure curve for all vascular beds. The ideal way to obtain such a Gaussian distribution is to use pressure data or computer-generated data based on normal pressure variations obtained from awake individuals, i.e. so-called

biological variability. Such data has the ideal $1/f^{\alpha}$ distribution of pressures necessary to generate the full flow-pressure curve to recruit the vascular bed. Therefore, generating a quasi-Gaussian curve of pressures when controlling flow with a perfusion pump will improve flow to all vascular beds, over and above prior claims for CPB.

A BVP module can be used to advantage in accordance with the present invention in the following additional specific applications:

1. Administration of Cardioplegia Solution: When cardioplegia solution is administered using a BVP module, improved protection of the myocardium occurs. Diastolic stiffness is less by BVV administration of cardoplegia (see Fig. 8.

2. Administration of Preservation Fluids to extend ex-Vivo Organs for Transplantation: When ex-vivo organs are planned for transplantation, perfusion with appropriate solutions using a BVP module can extend their ex-vivo life. This application permits a wider distribution of ex-vivo organs for transplantation.

3. Renal Dialysis: Improved dialysis for patients with renal failure is possible by perfusion of the dialysis membrane using a BVP module.

EXAMPLE

This example illustrates the use of BVV employing the low ventilation approach of NHLBI.

Our approach can optimize ventilation at low tidal volumes similar to those chosen from the NHLBI study (ref. 3) to maintain plateau pressure less than 30 cm H_2O by choosing the point of maximal curvature of the P-V curve (V_c - $V_{1.317d}$). Ventilation about this point is where recruitment can be optimized with biologically variable ventilation (BVV) because non-linear recruitment is greatest above the point and decruitment is minimized below this point.

Curve fitting from static P – V data is shown in the curve of Figure 7. Data was downloaded from a data acquisition system as described in the aforementioned US Patent No. 5,647,350 to a program for non-linear regression analysis. Data was fit to the Venegas equation (refs. 4, 6). Calculation of the equation was based on curve fitting to the Levenberg - Marquardt algorithm.

When airway pressure is at c - 1.317 d, the point of maximum compliance increase (P_{mci}) occurs. In this example, the tidal volume was calculated to be 295 ml.

The animal weight (pig) was 30 kg and hence the tidal volume chosen was 9.8 ml/kg. The minute ventilation set for biologically variable ventilation (BVV) in accordance with USP 5,647,350 was then determined to be the centering respiratory rate x tidal volume, 20 breaths/min x 295 ml = 5.9 l/min. In this example, at this minute ventilation, the tidal volume oscillated about a mean value of 20 with a range of 9 to 36 breaths/min. (refs. 13, 14, 20). Because P_{mci} is where maximal curvature occurs, an optimal increase is recruited tidal volume occurs by oscillating tidal volume about this point (refs. 4, 12).

SUMMARY OF DISCLOSURE

In summary of this disclosure, the present invention provides an improved control of the flow of a biological fluid to an organ utilizing a biologically variable control parameter, for example, biologically variable ventilation and biologically variable pulsation. Modifications are possible within the scope of this invention.

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CLAIMS

1. A method of controlling flow of ventilation gas from a ventilator device to the lungs of a body of a patient during controlled life support conditions, said ventilation gas being the primary source of gas to maintain life support to the lungs, said method comprising:

establishing a static pressure/volume curve for the patient in accordance with the relationship:

$$V = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

V = inflation volume

P = airway opening pressure

a = lower asymptote volume

b = total volume change

c = pressure at point of maximal compliance

d = value proportional to the pressure range of a straightline portion of the curve

establishing a predetermined pattern of variation over time of instantaneous respiratory rate and tidal volume from spontaneously-functioning normal lungs of a mammalian species,

selecting data from the pattern which satisfies the relationship $P = V_e \pm V_{1.317d}$ with respect to the pressure/volume curve, and

ventilating the patient in accordance with said selected data.

2. A method of controlling flow of a biological fluid to an organ during controlled life support conditions, said biological fluid being the primary source f fluid to maintain life support to the organ, said method comprising:

establishing for the patient by any convenient means in accordance with the equation:

$$F = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

F = organ flow

P = driving pressure

a = lower asymptote flow

b = autoregulated flow

c = pressure at point of maximal

d = value proportional to the pressure range of a straightline portion of the curve

establishing a predetermined pattern of variation over time of instantaneous changes in flow of a biological fluid to a spontaneously-functioning organ of a mammalian species,

selecting data which satisfies the relationship $F = \dot{V}_c \pm \dot{V}_{1.317d}$ with respect to the pressure/flow curve, and

controlling the flow of biological fluid to said organ during controlled life support conditions in accordance with said selected data.

3. The method of claim 2 wherein said biological fluid is blood and said organ is a heart of a patient and wherein said predetermined pattern is established by establishing a predetermined pattern of variation over time of instantaneous blood pressure and heart rate of a spontaneously-functioning healthy heart of a mammalian species.

4. Apparatus for controlling the flow of a biological fluid to an organ, which comprises:

means for establishing a static pressure/flow curve for the patient in accordance with the equation:

$$F = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

F = ~~biological fluid~~ organ flow ~~volume~~

P = ~~biological fluid flow~~ pressure

a = lower asymptote flow

b = autoregulated flow

c = pressure at point of maximal ~~compliance~~

d = value proportional to the pressure range of a straightline portion of the curve

means for establishing a predetermined pattern of variations over time of instantaneous changes in flow of a biological fluid to a spontaneously-functioning normal organ of a mammalian species,

means for selecting data for said predetermined pattern which satisfies the relationship $F = V_c \pm V_{1.317d}$ with respect to the pressure flow curve, and

means for controlling flow of a biological flow to said organ in accordance with said selected data.

5. The apparatus of claim 4 for controlling the flow of blood to a heart during controlled support conditions.

6. Apparatus for controlling the flow of ventilation gas from a ventilation device to the lungs of a body of a patient, which comprises:

means for establishing a static pressure/volume curve for the patient in accordance with the relationship:

$$V = a + b\,[1 + e^{-(P-c)/d}]^{-1}$$

where:

V = inflation volume

P = airway opening pressure

a = lower asymptote volume

b = total volume change

c = pressure at point of maximal compliance

d = value proportional to the pressure range of a straightline portion of the curve

means for establishing a predetermined pattern of variation over time of instantaneous respiratory rate and tidal volume from spontaneously-functioning normal lungs of a mammalian species,

means for selecting data from the pattern which satisfies the relationship $V = V_c \pm V_{1.317d}$ with respect to the pressure/volume curve, and

means for ventilating the patient in accordance with the selected data.

FIG. 1 (a)

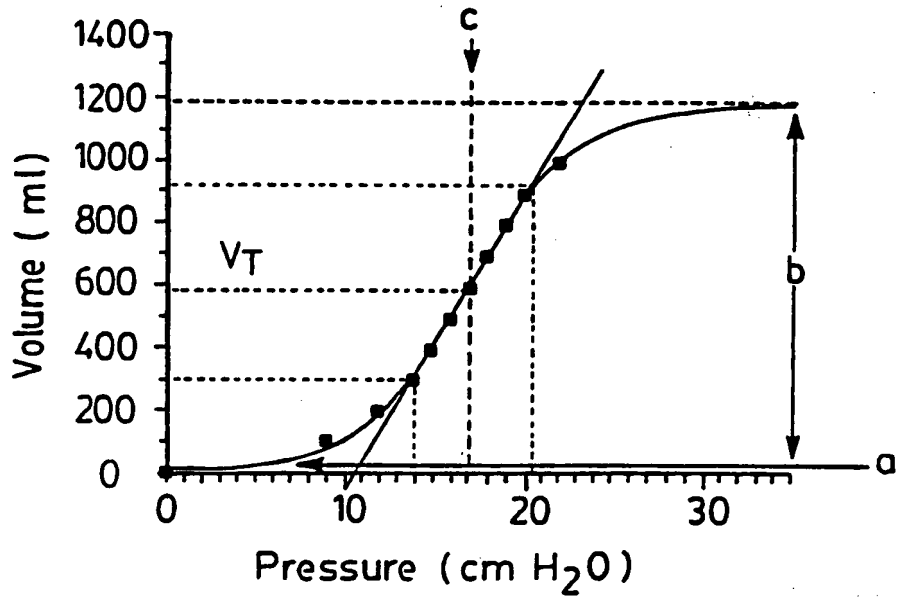
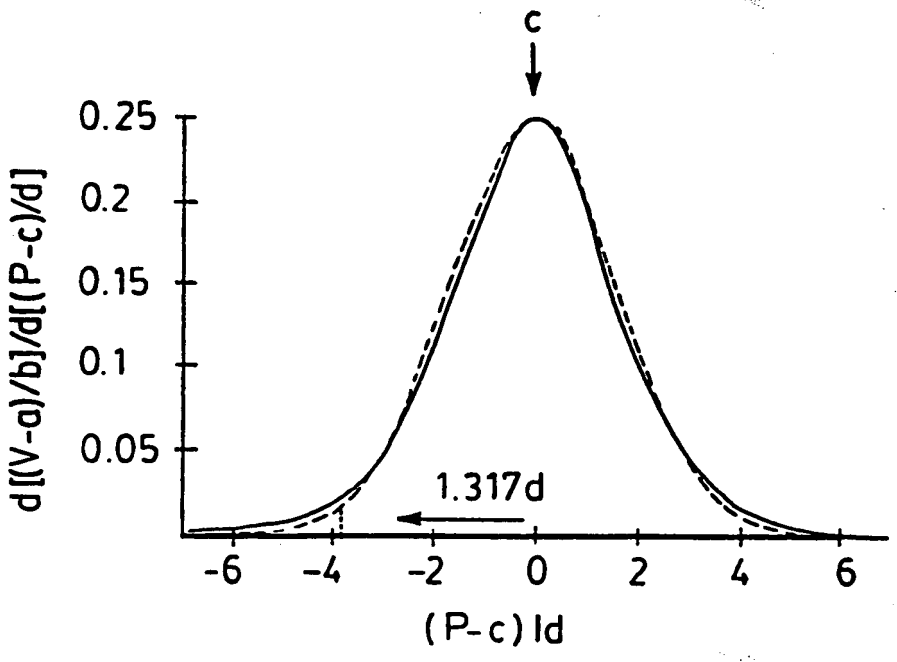

c
1400
1200
1000
800
600
400
200
0
Volume (ml)
V_T
b
a
0
10
20
30
Pressure (cm H_2O)

FIG. 1 (b)


c
0.25
0.2
0.15
0.1
0.05
d[(V-a)/b]/d[(P-c)/d]
1.317d
-6
-4
-2
0
2
4
6
(P-c) Id

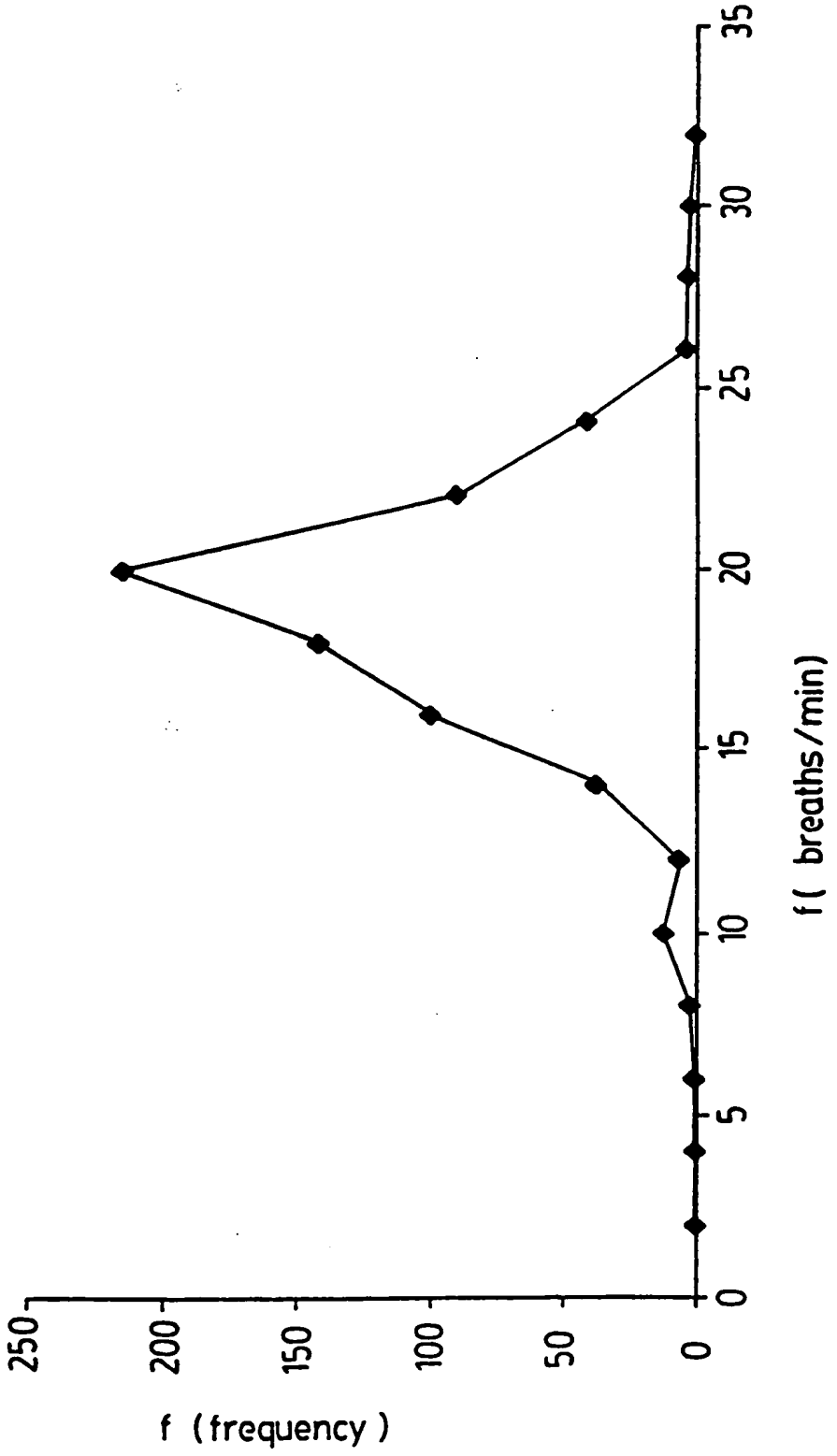

f (frequency)
250
200
150
100
50
0
0
5
10
15
20
25
30
35
f(breaths/min)

FIG.2.

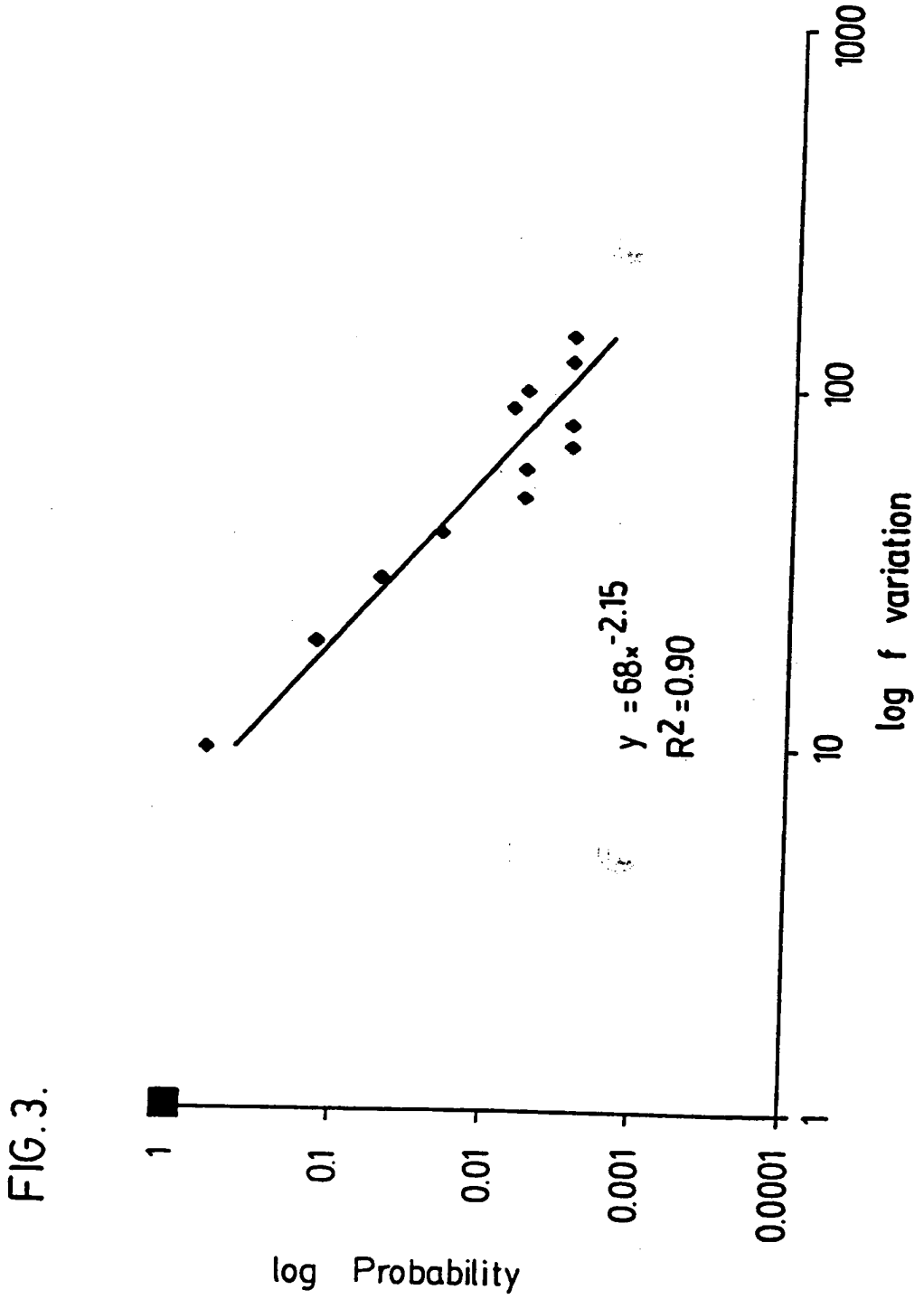

1000
100
10
1
log f variation
y =68x^-2.15
R2=0.90
1
0.1
0.01
0.001
0.0001
log Probability

FIG. 3.

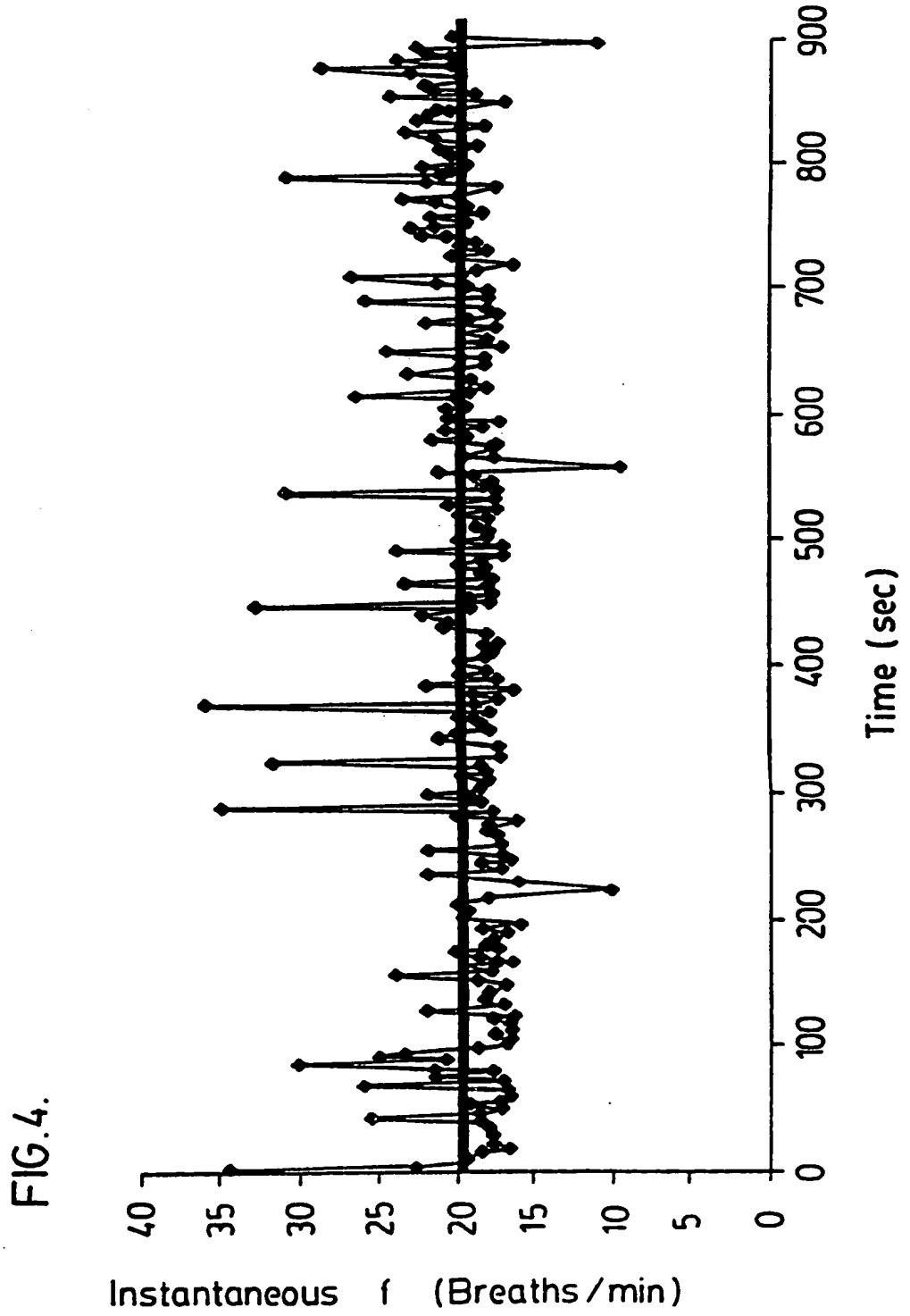

Instantaneous f (Breaths/min)
40
35
30
25
20
15
10
5
0
Time (sec)
0
100
200
300
400
500
600
700
800
900

FIG.4.

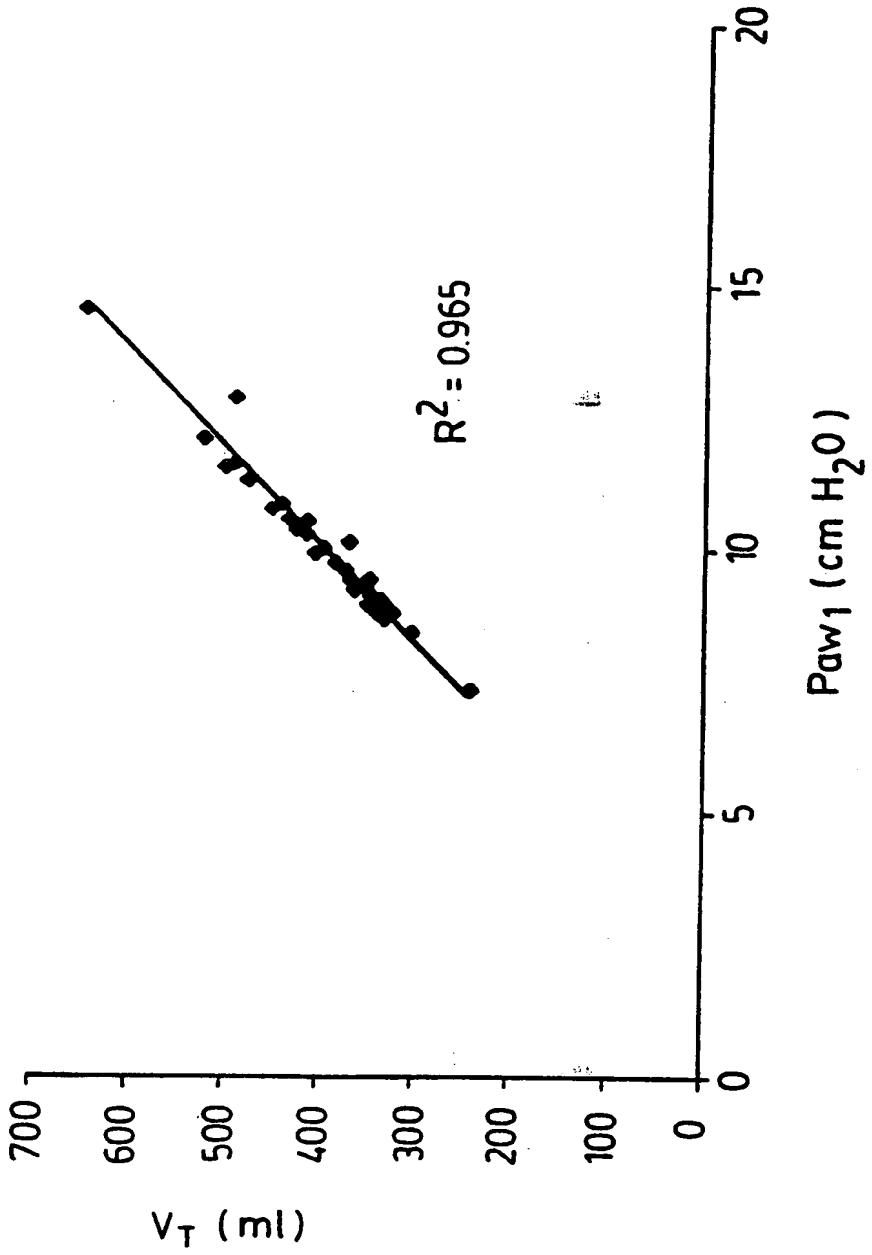


FIG.5.

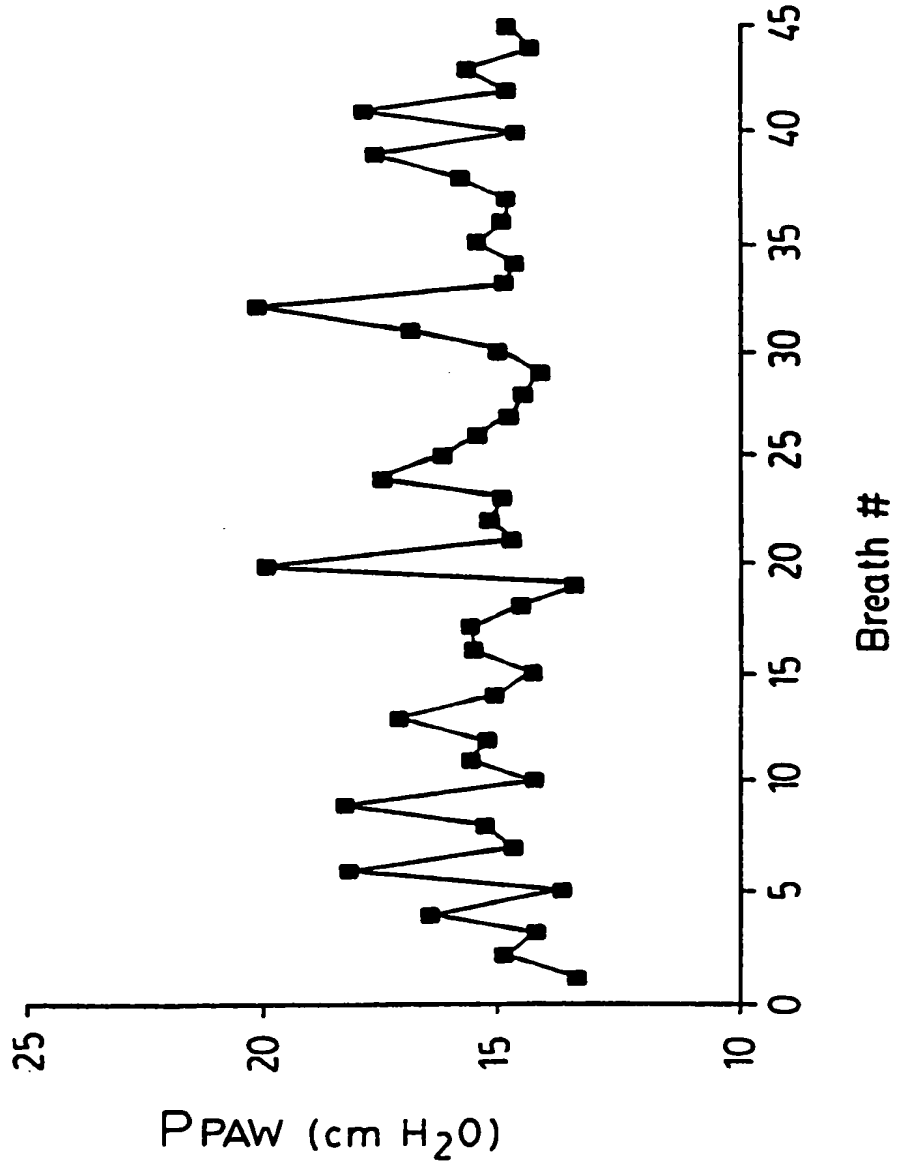


FIG.6.

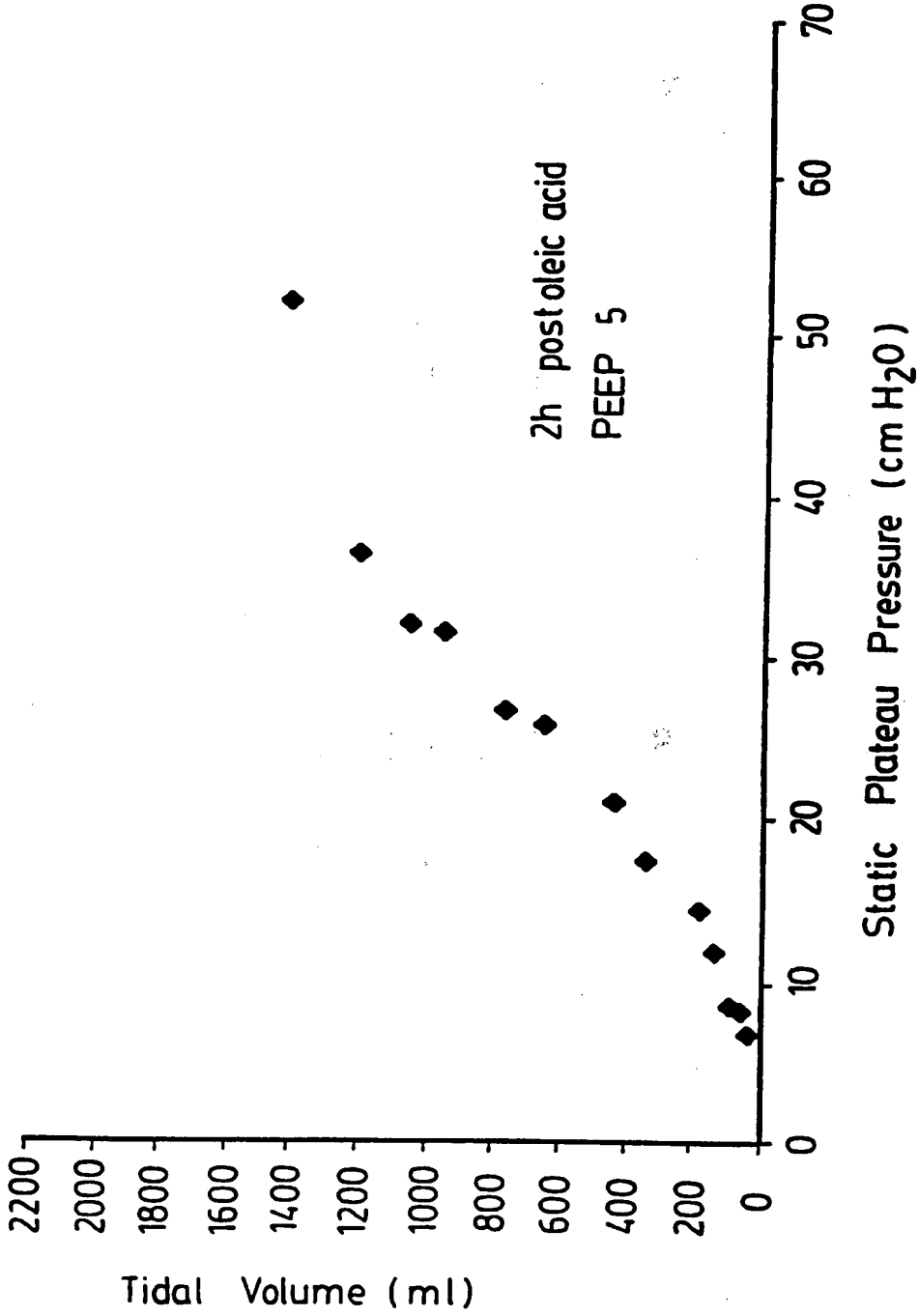

2h post oleic acid
PEEP 5
Static Plateau Pressure (cm H_2O)
0
10
20
30
40
50
60
70
Tidal Volume (ml)
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0

FIG.7.

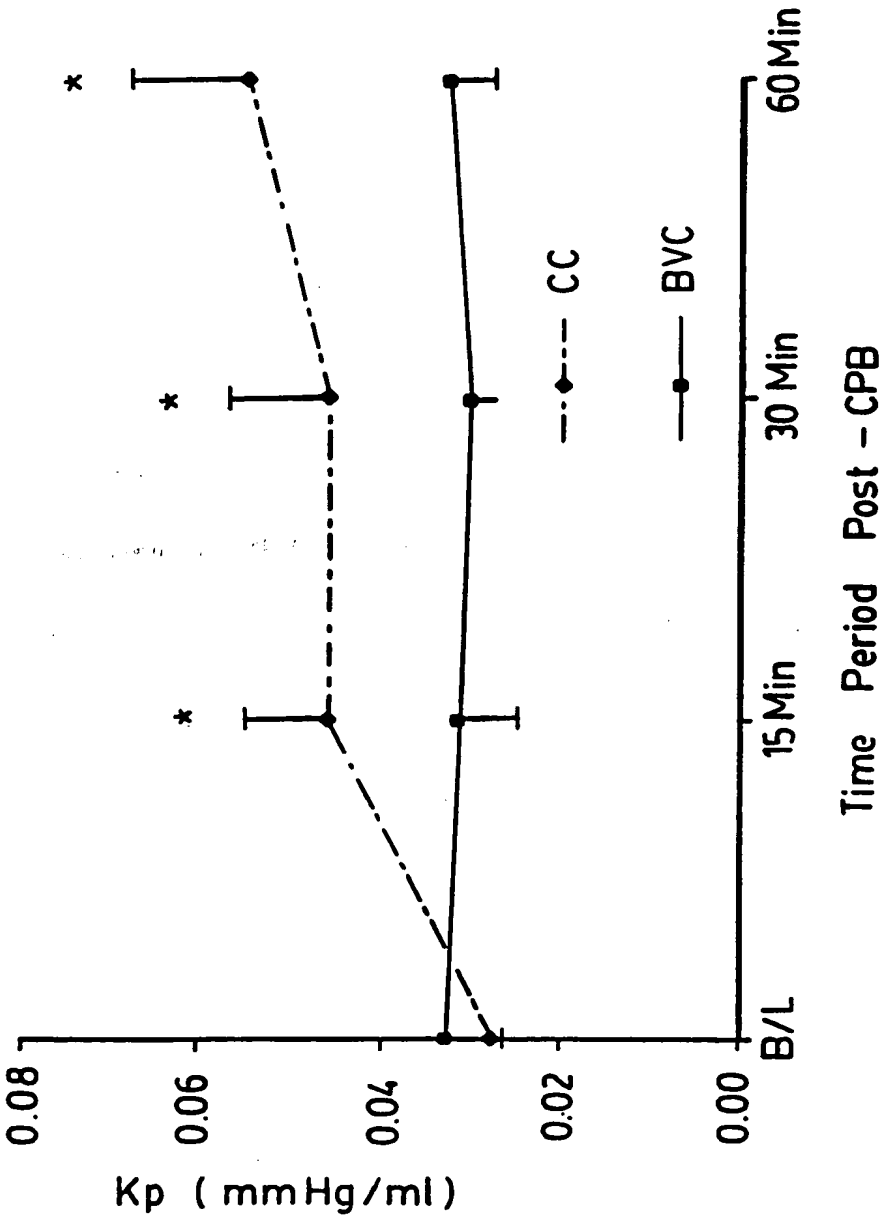

0.08
0.06
0.04
0.02
0.00
Kp (mmHg/ml)
B/L
15 Min
30 Min
60 Min
Time Period Post - CPB
BVC
CC
*
*
*

FIG.8.